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BODY:

U.S. SENATE JUDICIARY COMMITTEE HOLDS A HEARING ON THE LAW OF
BIOLOGIC MEDICINE

JUNE 23, 2004

SPEAKERS:
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HATCH: Good morning. I apologize for being late. This morning's been a very hectic morning for me, so I apologize to all of you who had to wait.

For those of you who came here for the previously scheduled judicial nominations hearing, let me just say this - boy, are you in for a big surprise. That's all I have to say. I just hope it's not too dull a surprise for you and that you enjoy a good debate over the proper reach of Section 505(b)(2) of the Federal Food Drug & Cosmetic Act. Today, the Judiciary Committee will consider a complex subject area that involves law, economics, science and medicine.

The purpose of the hearing is simple, although the law and science surrounding these issues are not. We will explore some of the key issues concerning the legality, feasibility and advisability of creating a new abbreviated regulatory pathway at the Food & Drug Administration for the review and approval of off-patent biological products.

First, for those of you who may not be sure what a biologic is, I would like to offer a simple working definition. Biological medicines are large complex protein molecules derived from living cells, often by recombinant DNA technology.

The area of biologics is of growing medical and economic importance. The biotechnology market posted a total of about $30 billion in sales last year, which is now expected to double to over $60 billion by 2010. We will see a concurrent explosion in the numbers of biologics. There are now over 150 FDA approved products on the market, with an additional 350 in various stages of human clinical testing, and over 1,000 others in the developmental pipeline.

But more important than commercial considerations, it is the hope of many that biological products such as those that may one day be developed from embryonic stem cells could lead to cures to many diseases that cannot be successfully treated today. Biopharmaceuticals appear to represent the future of medicine. For example, now that we have mapped the structure of the human genome, we are in a position to unravel the mysteries of the function of human genes and the proteins that they encode. Nothing less than a revolution in our understanding of human health and disease is well under way.

I am proud of the fact that scientists at the Huntsman Cancer Institute at the University of Utah are helping to lead the way. The old model of large patient populations, small molecule medicine is giving way to large molecule, small patient population therapies. The day may even come when individualized therapies will become common. These developments, of course, are not going to occur overnight, nor will they occur without great effort and ingenuity, and they will not be done on the cheap.

One thing is certain: When medical breakthroughs occur patients will want access to these new products, and their families and third party payers will want to pay as little as possible for them. Experts remind us that this new wave of therapeutic protein molecules is more complex to discover, manufacture and use than conventional small molecule drugs.

We know that many of these new biological products tend to be more expensive than old line chemically synthesized drugs. Some of these new wonder therapies cost over $10,000 per year or per course of treatment. For example, human growth hormone can cost $25,000 per year. Cost factors alone compel a thorough examination and public discussion of the merits of developing a fast track review and approval system that can reduce the price of biopharmaceuticals once patents expire.

Moreover, from a regulatory reform perspective, it should always be the goal of government to employ the least burdensome regulatory approach without compromising other important considerations, such as, in this case, patient safety and protection of intellectual property. Former commissioner of Food & Drugs and current CMS administrator, Dr. Mark McClellan, who took time from his busy schedule last week to visit Utah and meet with Senator Bennett and me and other Utahans on the new Medicare Drug Program, has recognized the confluence of medical, economic and regulatory forces at play.

Our society can ill afford to avoid a debate over the proper regulation of follow-on biologics. We simply cannot sustain over time programs such as Medicare unless we seriously explore what steps might prudently be taken to end an FDA regulatory system that effectively acts as a secondary patent for off patent biological products. Patient safety and product efficacy must remain at the forefront of this discussion.

The task before policy-makers is to consider how to maintain product safety and efficacy as we consider ways to eliminate unnecessary regulatory hoops for off patent biological product license applications.

I will stipulate that it will be difficult to manufacture some generic equivalents of off patent biologicals. Some products will, no doubt, be more difficult than others to reverse engineer. There will be technical issues galore. Some may actually prove impossible to duplicate without trade secret information. But from what I have heard, many products will be able to be safely duplicated.

I believe that many, if not all, follow on biologicals will require at least some form of human clinical testing. I also believe that the federal government would be very wise to consider providing taxpayer funding for the development of process validation guidelines that will help establish the critical manufacturing steps and assay parameters for medically or commercially significant off patent biological products.

I also think it would be wise to consider commissioning or otherwise sanctioning studies by organizations such as the United States Pharmacopeia or the Institute of Medicine, in collaboration with the FDA and other interested parties, to identify and address the technical issues that need to be resolved in order to fast track approvals for off patent biopharmaceuticals.

I have known and worked with Acting Commissioner of Food & Drug Administration Crawford for many years. I appreciate him and the service that he has given to our country. And I look forward to working with you, Dr. Crawford, and other experts at the FDA on this important issue.

I know that Dr. Crawford will make this an important priority and look forward to seeing the draft guidelines when they are issued later this year. I trust the chief counsel, Dan Troy, and Deputy Commissioner, Emmett Sustev (ph), and Liz Dickinson and Jerilyn Dupont will provide sound legal and policy advice. I have great faith in all of them.

As a co-author of the Drug Price Competition and Patent Term Restoration Act of 1984, I currently believe that whatever we do on the legislative front should observe a principle of attempting to balance incentives for both pioneer and generic drug firms. And while I am all for rolling up our sleeves to work to help develop an abbreviated approval system for off patent biologics, we must be properly respectful of the intellectual property of the research-based firms, because this is what undergirds the whole pharmaceutical enterprise.

And as we proceed into this new era of drug discovery, it is important to ask whether our current intellectual property laws relating to pharmaceutical research and development are adequate to promote the large molecule, small patient population medicine in the future.

For example, I have long thought the way we treat process patents under Hatch-Waxman should be reexamined in this new era of patient population medicine in which process patents will become more important and in which the relative importance of such patents will increase.

Difficult policy questions will crop up in a very difficult climate for the research-based pharmaceutical industry, of course, everybody's favorite whipping boy in an election year. Senator Lieberman and I have advanced an aggressive set of private sector incentives in our bipartisan bioterrorism bill. I plan to hold a hearing on the Lieberman-Hatch bioterrorism Bill, and we urge that all interested parties -- we urge them to review the IP provisions of this legislation and help us to get it right in every way.

Twenty years ago, we faced many challenges in fairly balancing the incentives and various interests when we came together on Hatch- Waxman. Frankly, I recognize that many in the biotechnology industry believe that the creation of a

fast track approval process for off patent biologics is the worst nightmare of a highly competitive, inherently risky industry, struggling to attract new capital necessary to bring new products to FDA approval and into the marketplace.

Let me close by suggesting an alternative and perhaps preferable strategy to scorched earth litigation. Rather than just saying no, please consider engaging in a constructive public policy dialogue that focuses on identifying the legitimate scientific and legal obstacles that must be overcome in order to create a fast track approval system for off patent biologics. At the same time, come forward with ideas that will improve the legal environment for pioneer biotechnology firms. That is what we did back in 1984 and that is what we can do today if we all work together on follow-on biologics and other matters. If we have the right balance in the law, the American public will certainly benefit. It only stands to benefit.

So, this is a very important hearing. The information that we'll receive here today will go a long way, I hope, to helping us to resolve these problems. But this is one of medicine's most important areas of study, and it's one of the most significant areas of problematic work that we have ahead of us. And I just hope that we can all work together to do this in the best possible way and that we can keep this out of the realm of politics and put it in the realm of doing what's right. And if we do that, this country will continue to be the major leader in the world and will do a great deal for people all over the world.

With that, I apologize for taking so long, but I had to get these ideas out. And hopefully they will get out so that people can help us to do a better job here. And we'll turn to our Democrat leader on the committee, Senator Leahy.

LEAHY: Well, thank you very much, Mr. Chairman. And I don't think any apologies are necessary. I think it's an extremely important issue, and I applaud you for holding this hearing.

Dr. Crawford, it's good to see you. I should note that Commissioner Crawford and I worked together a whole number of agricultural food safety issues when I was chairman of the Agriculture Committee and you were at USDA. It is good to see you again. It was always good to see you back then. And I should note, Mr. Chairman, that Dr. Crawford and I were adding up the number. He's got one more grandchild than I do, but both of us put together don't begin to match you. So we'll give you the crown on that one.

Biologic therapies fight life-threatening diseases and disorders. I think we should all understand that. In many cases, these therapies are orders of magnitude more effective than drug therapies. Let me talk about the most famous biologic treatment, which saved millions of lives. It's eradicated epidemics which in the 1930s and 1940s created mass panics each summer. Indeed, the first major outbreak of polio in the United States was in Vermont during the summer of 1894. Go around to some of our graveyards and you see a reference to that.

And rather than using the powerful tools of molecular biology physicians back then willy-nilly came up with therapies such as concocting an emulsion from the ground-up spinal cords of polio- infected monkeys. They added other chemicals, a witch's brew.

But one researcher, Dr. Jonas Salk, added formalin to the mix. Of course, the rest is history. It's changed the lives of people for the better all over the world. I'm old enough to remember when the summer with all the municipal swimming pools would close and all the rest, the little iron lung things to put your money in for research.

Well, today, research for new biologic therapies is no longer an endless guessing game. Potent new technologies hold the promise to develop completely new classes of therapies to prevent, treat or cure otherwise inevitable or untreatable or incurable diseases. These new technologies are being focused on the horrors of cancer, cystic fibrosis, hemophilia, AIDS, Alzheimer's, multiple sclerosis. That's just some of the many areas.

For example, breakthrough biologic therapies such as Avastin starve cancer tumors of the blood supply that they need to grow. Activase greatly reduces the otherwise permanent disabling effects of strokes in adults. Biologic technologies also hold out the best hope for those suffering from certain rare disease that afflict 25 million Americans, 58,000 Vermonters in my little state.

But biologic therapeutics often cost far more than traditional drugs. One reason, they're a lot more complex chemically. They're more difficult to manufacture. And I think we have to address this approval issue now because the patents of many biologic therapies are going to expire in the next few years.

With respect to drugs, Chairman Hatch and Congressman Waxman played crucial roles -- I can't overstate what they did -- their crucial roles in developing a fast track process to get less expensive, safe and effective generic drug alternatives into the marketplace under the Hatch-Waxman law.

But a clear fast track pathway doesn't exist for biologic therapies under our current law. So the critical question we face today is, should Congress design a fast track process for generic versions of these biologic innovations. My own answer is yes, but only if what we do is based on sound science, if these alternative therapies are safe and effective, if they'll help prevent shortages, and these biologics would provide less expensive but potent alternatives for consumers.

I know that generic biologics are now available in Eastern Europe and Asia. Many point out these biologics have been safe and effective, are less expensive than the original product in those countries. Others urge we cannot be sure of the safety or legality of these products. It may be that a sliding scale approach is needed for the U.S. Perhaps the level of scrutiny should intensify with the increasing complexity of the molecules involved, the sensitivity of the formulation process, the risks of deviation from the patent process.

Now science has to rule this decision, not politics, not greed, not the clout of the powerful vested interests. We need to do the right thing for millions of infected families. They're depending upon us to do the right thing. So I do want to work together to find a faster way to get more of these valuable therapies available at lower prices to consumers without sacrificing safety.

You know, the people that have these diseases, whether it's Alzheimer's, multiple sclerosis, some of the other things I mentioned, nobody asked whether they're Republicans or Democrats or independents. They're Americans. And throughout the rest of the world there's so many millions more who are affected. We in this wonderful great country can now find the cures. We can do so much for the people of our own nation but throughout the world, as we did with the polio vaccine. So I hope all the stakeholders will participate in this process.

The testimonies of Dr. Ben-Maimon and David Beier present a useful point and counterpoint on both sides of this issue. Mr. Beier also raises complex trade secret issues. The bottom line, of course, you have to have a careful balancing of interest in recognition of patent and trade secrets. But we need to work together for the families that are going to be helped by this approach. I'm glad we're beginning this.

Again, I applaud the chairman for starting these hearings. He knows and I know it could be a long road, but it's one where we all have to work together. The benefits to the people of this great country are so huge if we do it right. So thank you, Mr. Chairman, for doing this.

HATCH: Well, thank you, Senator Leahy.

Let me welcome our distinguished witnesses here today.

On the first panel we will have the Acting Commission of the Food & Drug Administration, Dr. Lester Crawford. We welcome you to the committee once again, Dr. Crawford.

Dr. Crawford has a distinguished career, and we value his leadership in protecting the public safety. Most recently he worked very hard to protect the U.S. food supply from the threat of mad cow disease, and we are all grateful for his efforts.

In addition, I went to the opening ceremony for the new unified FDA Life Sciences Building, for a laboratory that is being built at the White Oak campus to replace the 38 different buildings throughout the region that are currently used for FDA offices. It's really a very, very impressive facility. And I encourage all my colleagues to visit. And of course, it's just the beginning of that White Oak campus, but once we get that built, and that's pursuant to the FDA revitalization bill we passed over 10 years ago -- once we get that built there is no place in the world that will be able to compare from the food and drug regulatory standpoint with FDA. And that's long overdue.

I also want to extend a warm welcome to Dan Troy, who's accompanying Dr. Crawford this morning. Mr. Troy is the chief counsel for the Food & Drug Administration.

And these are two great public servants, and I just want everybody to know it.

So, we'll turn the time to you, Dr. Crawford. We really appreciate the service you give.

CRAWFORD: Mr. Chairman and members of the committee, I appreciate very much the opportunity to be here and to participate in this important hearing on the subject of follow-on proteins.

FDA and the Congress share a great concern for senior citizens and other patients who have difficulty paying for prescription drugs. FDA has taken a number of significant steps to promote greater access to affordable prescription

medications, including unprecedented steps to lower drug cost by helping to speed the development and approval of low cost generic drugs.

Since its enactment in 1984, Hatch-Waxman has governed generic drug approval process. In general, the law has been working well. Since 1984 over 10,000 generic drugs have entered the market. And generics now account for close to 50 percent of prescriptions filled. The agency is now approving generic drugs on an average rate of one per day.

CRAWFORD: Medical innovation is a complex process, but one that can bring great value to patients. To realize the full benefits of medical innovation, it is important to adopt policies that protect incentives to develop new drugs and medical devices. Achieving this goal requires a delicate effort to strike a proper balance. Promoting innovation requires the right mix of incentives, safeguards and effective regulation to secure maximal benefit from safe and effective new medical technologies while assuming mechanisms for broad and equitable access to these new treatments. FDA has different statutory approval mechanism for drugs and most biological products. I say most biological products because many biological products are also drugs as that term is broadly defined in the Food, Drug and Cosmetic Act.

Traditionally, some natural source proteins have been regulated as drugs, including insulin and human growth hormones, while other natural source proteins, such as blood factors, are regulated as biological products. Currently some proteins are licensed under the Public Health Service Act and some are approved under the FD&C Act. FDA approves new drugs, as distinguished from biological products. under approval mechanisms found in Section 505 of the FD&C Act and licenses most biological products under Section 351 of the PHS Act.

Full new drug applications under Section 505 of the FD&C Act and biologics license applications under the PHS Act require submission of complete reports of clinical and animal data to support approval. For drugs approved under the FD&C Act, manufacturers can apply to FDA under Section 505(j) of the FD&C Act for approval of generic versions of the brand products after the patent and other exclusivity periods expire. This process is known as the abbreviated new drug application, or ANDA, process.

Section 505(b)(2) also provides for the approval of NDAs supported by the scientific literature or by FDA's earlier finding that a drug is safe and effective. Both the ANDA and the 505(b)(2) approval processes incorporate consideration of the innovator's intellectual property rights into the drug approval process.

The ANDA process in Section 505(j) was established through the 1984 Hatch-Waxman amendments. This is an abbreviated approval mechanism for generic versions of drugs approved under Section 505 of the FD&C Act. The ANDA process does not require the drug sponsor to repeat costly animal and clinical research on ingredients or dosage forms already approved for safety and effectiveness.

By establishing that the drug product described in the ANDA is the same as the innovator drug product approved in the NDA, the ANDA applicant can rely on the agency's finding of safety and effectiveness for the drug. The FD&C Act provides the ANDA and 505(b)(2) abbreviated approval pathways for drugs approved under 505 of that act.

However, the PHS Act has no similar provisions. The approval of generic or follow-on protein and peptide products has both scientific and legal dimensions.

First as a scientific matter, FDA believes that for some protein products, regulated under 505 of the act, science has progressed sufficiently that we are able to assess the degree of similarity or identity between the innovator and a follow-on product. Prior to publishing a draft guidance document, FDA intends to have a major scientific workshop in conjunction with the Drug Information Association to explore this issue. FDA is still considering a separate process to address the legal and regulatory issues.

Today's hearing is an important part of that discussion, and I thank you, Chairman Hatch, for holding it.

HATCH: Thank you, Dr. Crawford. In your testimony you talk about many unanswered scientific, legal and policy questions about the follow-on versions of biological products approved under Section 351 of the Public Health Service Act that must be explored, and that the FDA plans on promoting public dialogue on these questions. Now, what do you anticipate some of these questions to be? And how will FDA promote public dialogue to find answers to these questions?

CRAWFORD: Well, what we'll do -- as I announced, we're going to have this scientific workshop, which will be joined by the Drug Information Association. And it will be a well-managed workshop where questions will be posed to the participants. And they will be structured in such a way that we can come out with a set of common understanding about what is needed in order to regulate follow-on proteins, as they're generally called. We also will get information

from deliberations that the European Union has had on this same subject and also from other trading partners around the world.

But what we really need is to determine how do we go through the scientific and regulatory process of ascertaining that a product is either identical or has enough characteristics in terms of the active ingredient of the molecule to where we can declare it is in fact worthy of consideration as a generic.

The term generic, as you know, essentially means the same. And so, we -- and we're not sure with the kind of science that we have that in fact we are ready for that kind of determination with many of these large molecules, as you put it in your opening statement. So we need help in this direction. FDA has not made its mind up about it. We need to know more about this science.

We find, as you know, that we get great answers from industry because they are dealing with the problems every day. And we look forward to involving them in this process as well as the academic, medical and scientific communities.

HATCH: As you know, the cost of prescription drugs has been an issue of importance to many Americans, and Congress has been -- we've been working on various legislative proposals to try and address this matter. I believe that enacting the Medicare Prescription Drug Law last year was a step in the right direction. All Medicare beneficiaries will soon have access to the Medicare Prescription Drug Program and lower income beneficiaries will receive significant help and relief from their drug expenditures.

The Medicare Prescription Drug law encourages drug plans to offer generic drugs to Medicare beneficiaries when appropriate, which is one important way to find savings.

Now, in fact, in your testimony you state that generic drugs typically cost 50 to 70 percent less than their brand name counterparts and that they are bioequivalent. Now, according to the CBO, generic drugs save consumers an estimated $8 billion to $10 billion a year at retail pharmacies. And I was told by Mark McClellan just a few days ago that actually that figure is even higher today. As a result of Hatch-Waxman, the consumers are saved.

Now, do you believe that generic biologics, if they can be developed, would provide Americans with similar savings?

CRAWFORD: I think it's too soon to say. As I mentioned, the European Union is moving in sort of the same kind of direction. But no country or group of countries has experience with this to the extent that they can say what the savings would be.

These are difficult molecules, as all of you know, to characterize. And so how many generics, if you will, once we work out the regulatory and scientific issues, will enter the market for each one that is approved as an innovative product, we can't say at this time. We do know that some biologics, as you mentioned, are very costly indeed. And so, even the introduction of one other competing product will surely lower the cost, but it's not possible to say whether or not it'll be the same percentage as the 50 to 70 percent figure that we have with standard drugs.

HATCH: OK. Now, to what extent do you think that Section 505(b)(2) of the Food, Drug and Cosmetic Act applies to biologics? Now, you might want to have Mr. Troy help us with that one.

CRAWFORD: I very much want to have Mr. Troy join me. He's our chief counsel.

HATCH: Well, I think it'd be good to have his testimony on that.

TROY: Thank you, Senator Hatch.

505(b)(2), by its terms, applies only to the Food, Drug and Cosmetic Act and to 505 products. FDA does not believe that 505(b)(2) applies by its terms to products that have been approved under Section 351. But, as Dr. Crawford mentioned, there are a variety of proteins -- human source proteins -- insulin, human growth hormone and others -- which have been approved under the 505 pathway, in part some of these, for historical reasons. And so, where the science and the law is there, we believe that follow-on proteins may perhaps be approvable using 505(b)(2).

HATCH: That's helpful. Just keep helping us up here to understand this, OK, because this complex to all of us.

Senator Leahy, if you care to ...

TROY: Sorry, I talk too much like a lawyer sometimes.

HATCH: I'm glad to hear that, to be honest with you.

LEAHY: You'd be surprised the numbers of lawyers who show up here, at all kinds of hearings, and some even on this side of the dias.

(LAUGHTER)

HATCH: And I can say some are better than others too.

(LAUGHTER)

LEAHY: It's true. Of course, those on this side, both Republicans and Democrats, are the best, but that's OK. Although I must admit there are days when I'm here, I miss those days in the courtroom.

You know, Commissioner Crawford, as I said earlier, it is good to see you again.

CRAWFORD: Thank you, sir.

LEAHY: And I've always enjoyed working with you.

In your written testimony, you raised concerns about being able to assess the relative sameness of generic alternatives that derive from biological sources because of the complexity of protein structures. But then you state, "However, the science of characterization has progressed to the point where it's becoming possible to make such assessments for some products, and we expect that science will continue to progress."

Some of the European and Asian countries would say they're ahead of the U.S. regarding developing an accelerated process to approve these generic biologics. Are you considering recommending to OMB any legislative proposals for Congress to review to take advantage of the technological advances, those that might allow scientists to make accurate sameness evaluations?

CRAWFORD: We're not at this time proposing legislation. As I mentioned, we're going to have this scientific workshop in conjunction with the Drug Information Association. And at the conclusion of that, we'll weigh what we've found out and determine which fork in the road to take. But at this point, we're not prepared to say whether or not we would be ...

LEAHY: Well, after that, could you let Chairman Hatch and myself know where you're going with it? Because at some point -- and it'd be nice to have us all on the same hymn book, the Congress ...

CRAWFORD: Absolutely.

LEAHY: ... and the administration. There is going to be required some legislation.

For example, David Beier's testimony raises some concerns about protecting the confidentiality of proprietary business data and trade secret information. He pointed out the FDA recently noted the data required for the approval of any new product must be in the public domain.

How do you handle trade secrets and proprietary information? I mean, you have to do your job, but the companies have to be assured that they're spending millions of dollars on something, that their confidential information is kept confidential. How do you do that balance?

CRAWFORD: I'm going to ask Dan to comment on that. But before he does, ever since I was first in the FDA in 1975 we -- as you know, we have had great difficulties as the science changes and so forth in maintaining the confidentiality. But FDA has always had as a top priority the maintenance of trade secret information, and I think our record is quite good on that.

Dan?

TROY: I want to pick up on what Dr. Crawford said. Congress has decreed that trade secret and confidential commercial information is not disclosable by us. Indeed, it is a crime to disclose trade secret information under an act of Congress.

And I think as a result of that, one of the most salutary aspects of FDA's culture is the care that people at FDA take with the very valuable business information that is entrusted to us. I think people really have an appreciation about how valuable it is. I'm not saying there are never any missteps. But by and large, there's a really good culture there of protecting that confidential commercial and trade secret information.

The upside of that, of course, is that companies develop that information and can submit it to us with a fair degree of confidence that we're going to preserve it. Of course, as comes up in, for example, the whole debate about clinical trials, at times there are profound interests on the part of people in the patient community, the medical community, the scientific community, who want access to that information. And there's no doubt that that is a tension that we have to navigate.

And I think it is a tension that comes up in this context as well. On the one hand, if we don't develop -- if we don't preserve this intellectual property, then people aren't going to do the work to develop the new products. On the other hand, if we give perpetual protection to the intellectual property, then you'll never have follow-on proteins or generic biologics.

The brilliance of Hatch-Waxman is that it struck a balance between innovation and intellectual property protection and, at an appropriate time, a pathway for allowing products to come to market that are less expensive and more affordable and more available. And so, it is precisely that balance between innovation, which in this industry primarily manifests itself as intellectual property protection, and affordability that we are going to strive for and we're going to work with Congress to strive for because I think there's a pretty broad agreement that we're not going to be able to do this alone.

LEAHY: Thank you. What I'm going to do -- Senator Hatch has to leave for a vote. He's coming right back. I have another committee. I have to leave for a similar thing. You're both aware of how they usually try to have us on 12 different things at once, especially as we come close to a time, as we are, when there's going to be a break. So, I'm going to turn it over to Senator Durbin. And it's all yours. Wreak all the havoc you want.

(LAUGHTER)

DURBIN: Be careful what you wish for.

Let me thank the witnesses for being here and especially thank the FDA as an agency. The time I've served on Capitol Hill, I've had a good working relationship on the Appropriations Committee with the FDA.

And Dr. Crawford, I thank you.

CRAWFORD: Thank you, sir.

DURBIN: Mr. Troy, we're not -- we don't have a long friendship or relationship, but I'm glad that you're here today, and I thank you for your testimony.

Let me try to explore an element here that I think needs to be discussed, and that is the market dynamic -- and I think, Mr. Troy, you alluded to it -- to protect the intellectual property of the company that discovers the chemical drug or the biologic drug, but only to a certain point, at which we decide that their vested interest in that property becomes a public interest.

And we move through Hatch-Waxman in 1994 to the belief that generic drugs are of public value because they save consumers money. You referred to the brilliance of Senator Hatch, and I think he caught that as he was leaving the room, and I hope he did. And I want to give credit to both him and Congressman Waxman.

But it is also true from your testimony, Dr. Crawford, that this was not an altogether smooth transition. There was some resistance from some pharmaceutical companies under Hatch-Waxman, which led to the 2003 directive from the FDA concerning how long you could contest the movement from brand name to generic. And that, I think, had become abusive. The conduct of the industry had become abusive.

So, address for me, if you will, for a moment the market dynamic when it comes to this issue. Are we not dealing with the same thing, that the original company that has developed the protein or the biologic has a market interest in maintaining exclusivity in terms of production as long as possible, because it is a profitable thing, and that we understand that at some point it may move to a generic or follow-on at lower cost.

You have addressed, at least alluded to, the scientific challenge of producing the follow-on in a product that is different than some chemical drugs. But speak to me as well about the market aspect of this. Are you -- what kind of resistance is the FDA running into from those who have patent on the original biologic and the profitability of that medicine, who believe that moving to the follow-on is going to end their profitability? Is there a resistance there that is part of this equation?

CRAWFORD: Well, what we have heard -- there's a great deal of interest in what we're doing here, it is fair to say -- but what we have heard from the industry and the relevant trade associations is that I think there's a willingness to help FDA define through appropriate intercourse what it is that we need to do in order to ascertain that there is sufficient sameness between the pioneer product and the generic product to allow the process to move in a fair and equitable manner.

We're going to need cooperation from industry, but also from manufacturing experts, the academic community, chemical, medical community and so forth. So, we have got to start this dialogue. And I don't really know where it's going to end up, but we're going to open up with this scientific workshop and then that's going to lead us into other directions.

At the same time, we're going to have a separate consideration of the legal and regulatory aspects. But I think we've got to get the science first. So to answer your question, I wouldn't call it a resistance, but there is a great deal of interest in what we're doing. And I think the public in general wants to be part of the process, and I think that's a good sign.

DURBIN: How important is the cooperation of the brand name biologic manufacturer in developing the science and developing the process that leads to the follow-on biologic?

CRAWFORD: Well, I'm going to ask Dan, if I may, to respond to that. But obviously the attitude of the industry, both in the pioneer companies and also the -- those that are seeking to get a generic status, there's a tension there and there also is an interchange, which sometimes is dictated by the courts, as you know, that is very important to the process.

Dan has had a great deal of experience over the last three years dealing both in courtroom situations and also in adjudication in some of these disputes. And he is an expert in this area of the law, so I'd like to ask him to comment.

TROY: Thank you. I think it's actually a bit of a mistake to suggest that the innovator industry, at least from what I've read and what I've heard, is united on this issue. There are -- I think there are different camps that people fall into, that different companies are looking at different positions. And so, I don't think what we're seeing is some uniform innovator brand company resistance fighting this issue tooth and nail. I think there's a recognition that sooner or later the time is going to come. A lot of it will depend, of course, on the science.

When you say we need the cooperation, ultimately of course for -- you can pass legislation with or without somebody's cooperation. Normally you get someone's cooperation to one extent or another. Ultimately we can -- we do administer Hatch-Waxman, one might say with the cooperation of the brand industry. They give us the data to approve their product, then we can and do, under Hatch-Waxman, rely on that data in approving an ANDA. They don't play any role in that process at that point. On occasion they might raise scientific or legal objections to what we're doing.

We are pretty good, I think, at separating out the wheat from the chaff and recognizing when challenges are being raised that are frivolous or challenges that are raised that are real and substantial that we need to deal with.

So I think that, as Dr. Crawford reflected, we're still at a very nascent stage. We're exploring. I think people are figuring out where they are. There's a lot -- there's still just a lot of public process to undergo and a lot of scientific and legal and regulatory exploration.

DURBIN: If I can ask one last question, Mr. Chairman. This is a question which relates to your agency, Dr. Crawford. And it relates to this issue certainly, but many others.

Having watched your agency over 20 years and watched its budget, I continue to marvel at how much you get done for the amount of money that we send out to you and how much we rely on you to get it done, whether we're talking -- the approvals from -- as you know better than most, that just involve virtually every aspect of the human life, the FDA is in there and involved in it.

And so, when we talk about this kind of undertaking, which is clearly going to require some of the best and brightest, talk about whether or not we can develop a scientific process and say with some certainty that there is a follow-on biologic that can be trusted and is it a lower cost, where do you stand in terms of resources, particularly in personnel and lab space and whatever is necessary to meet this challenge and so many others that we throw your way?

Senator Hatch and I were on the floor yesterday talking about another issue, which we won't go into here, but one of the elements of it was, well, the FDA needs more manpower, more people to get this job done.

So in light of everything that Congress keeps heaping on your agency, FDA, including this, where are you?

CRAWFORD: Thank you for that question.

(LAUGHTER)

And it's certainly one that I can expand on as much as you like. Senator Hatch mentioned the White Oak campus. And the idea there is to get the expertise of FDA, at least on the medical product side, the three centers there plus the support staff above, including me, located in the same place so that we can have a critical mass of scientists, like, say, oncologists and, in this case, pharmacologists, people that work in biologics of all sorts.

If you can get them working on the same campus instead of -- actually, we have about 38 different facilities. If you count the Mayo facilities, we have 55 in the Washington area, and it increases every year a great deal. That is the single greatest impediment to our getting our job done.

We have committee meetings of very key people to review applications that involve 70-mile roundtrips for our scientists. And they generally have to travel on Washington's beltway system. So, you can imagine managing FDA, such as I'm charged to do, what a great difficulty that is.

Apart from that, there is good news. We are now up to the largest number of personnel that we've ever had in FDA. And the recent increase is due in large part to the Congress dealing with the bioterrorism problem and providing both funding and personnel to deal with that. So the big increase has been there and not in the medical product area. In other words, it's been in the field forces. But it's helped a great deal, because in the late 1970s we lost 10 percent of our personnel and then it has taken all this time to get them back up to that level, and we're now even past it.

The other good news is that Congress has allowed incentive pay and locality pay so that we're able to pay physicians, for example, and other health care professionals competitive salaries. They're low end competitive, to be sure. I wouldn't say that things are perfect there. But when we're about to lose someone to another company or even to another government or something like that, we are able by aggressively extending the authorities vested in my office to save a lot of these people.

And the turnover rate in FDA is -- down through the years that I've been associated with it, is -- a healthy rate, it's estimated to be about 8 percent. You need some turnover, as you well know, but you need to be -- what I need to be very careful of is whether that turnover is happening in key pockets. If the agency level is 8 percent and then in key scientific areas you're losing 25 percent to 50 percent a year, then you've still got just as big a problem. So far so good in that respect.

The two years -- two and a half years I've been back at FDA basically being the chief management officer, we have stabilized that very, very well indeed.

We do have a precarious level of budgeting. It's about $1.8 billion. And as you would know, that is absolutely -- we've got to make really good use of that. We have less and less discretionary funds. And we can't leave anything that we are charged with regulating high and dry. We have to retrain people and also multiply train them.

One of the things that has helped under the Bioterrorism Act is we have -- we're able to commission other agencies to do FDA's work in key spots. In order to cover the border with products coming in, not just foods but drugs and other things, we have taken major advantage of that provision, which was a great boom to FDA. And we have now commissioned 7,500 Customs and Border Protection agents to do FDA-type work. We do that after training, and we do that after staying in contact with them.

We also -- each year in the budget, we try to plan for things like BSE, the cattle disease. And I would give my predecessors a lot of credit for asking for the funding that we needed in order to stay up to date on that and to prepare for the inevitability.

So I'll stop there, but if you want more you can get it.

DURBIN: Thank you. Mr. Chairman, I think we all understand that as important as these discussions are, the implementation of our good ideas depends on the professional men and women at the FDA who can get the job done. And while you were out, we praised you. We lavished praise upon you for your work with Congressman Waxman. And your staff will verify that what I say is true.

HATCH: Well, that is unusual in this committee.

(LAUGHTER)

While I have you here, I want to take advantage of this for a minute because there are a couple other questions that I have that I hope will amplify. I know you're going to be holding a public symposium on follow-on biologics. I would like more details on the guidance your agency will be issuing on follow-on biologics.

The first and most important one, will this be issued? Secondly, what will be addressed in the guidance that you will issue? To me, this is an important matter, I think not just to me but to many people. And I'd be interested in your thoughts on that.

CRAWFORD: Well, what -- Senator Leahy, while you were out, also brought this subject up, and wanted to know what we'd find in scientific workshop. And I think what would be appropriate, with your concurrence, would be following the workshop, we should come down and brief you and your staff and other members of the committee, as appropriate and as they are interested, on what we do find and where we think it's going to lead us.

HATCH: Do you know about when that would be, when we would ...

CRAWFORD: Well, we hope to have the workshop by the end of the summer.

TROY: I think in the fall.

CRAWFORD: Your concept of fall and mine is different...

TROY: Yes, probably.

CRAWFORD: ... as a matter of fact because you're an attorney. I'm pressing, Senator, to have ...

TROY: It's a disability.

CRAWFORD: ... have it done maybe the day after Labor Day or something like that. And we will come see you when that does happen.

When we turn that into guidance will actually depend on what we find out through this fact-finding process. Again, we are pressing very hard to get something out. But I have to plead that we don't know what we will find out in the scientific workshop, so I can't project. We may find out -- we are open minded about this -- that the science is still lagging in terms of characterization of these products and so, we need to fund some research projects or something like that. So I have to answer it that way.

HATCH: Well, we'll be interested in what kind of policy you come out with, and let us know as soon as you can.

Could you give us more details on major policy decisions that we would face in devising a system to regulate follow-on biologics?

And then Senator Leahy mentioned trade secrets. Could you or Mr. Troy amplify on that and the other major issues that we'll all be facing?

CRAWFORD: Yes. I'd like to ask Dan to handle that part.

HATCH: OK.

TROY: I guess I'm not quite sure I understand what the question. To address what the trade secret issues are?

HATCH: Yes.

TROY: Yes, we talked about it a little bit while you were gone. Congress has prohibited us from revealing trade secrets, and we are very protective of trade secrets and confidential commercial information.

That said, at a certain point, information becomes sort generally known and generally known in the scientific community. And part of the challenge is figuring out at what point does information kind of cross over. Obviously, if there's literature about something, then that's easy.

But I think it's fair to say that the agency has always been extremely protective of intellectual property. That is one of our key missions. It is a key part of our culture. And the challenge going forward, which you're well aware of, because that's what you did in Hatch-Waxman, is to strike a balance between the intellectual property protections and making products accessible and affordable.

HATCH: OK. Well, one other thing: We're going to be holding a -- this committee will be holding a re-importation hearing in the near future. I'd like you to be ready to come to that. We're going to need your testimony on that.

CRAWFORD: Well, look forward to that. As you know, this has been something FDA's been heavily involved in for some time. And we look forward to some reasonable solution to it.

As you also know, our concern by statute and also by the thing that drives us to be public servants is the safety and effectiveness of these products. So we have concerns about that. We'd be very pleased to share that with the Congress, this committee and anyone else who's working in that particular area.

HATCH: Well, thanks, Dr. Crawford.

For the record, one of the questions that we may submit in writing -- and I'll keep the record open until the end of the day for any questions any member of the committee has on writing. But we'd like you to not only comment on trade secrets, but also any other major factors that will be discussion points on how to regulate follow-on proteins, if you can do that for us.

CRAWFORD: We'll be happy to respond to the question in writing, if we could.

HATCH: If you could, thank you. I appreciate it.

All right. We appreciate both of you being here. We think you're both great public servants and you've been doing tremendous work out there. And I can't wait till you not only have that central campus so that the administrators don't have to travel all over 38 different places all over this area, but you'll have the highest and the best scientific instrumentation and facilities to work in, which is something that we owe to you and that you need to have done. So I hope you'll keep the pressure on Congress to finish the White Oak campus.

CRAWFORD: Thank you for all your support, sir.

TROY: Thank you.

HATCH: It's good to have both of you here.

At this time, I would like to introduce our second panel.

First, we will have Mr. Bill Schultz who is testifying on behalf of the Generic Pharmaceutical Association. Mr. Schultz is a partner with Zuckerman Spaeder who practice in food and drug law, complex civil litigation, products liability and appellate litigation.

Mr. Schultz also was the Food & Drug Administration's deputy commissioner for policy and was responsible for overseeing the development of all FDA policies and regulations and FDA legislation. Most of us remember Bill when he was the FDA counsel to the former chairman of the Health and Environment Subcommittee of the House Energy and Commerce Committee. And while working for Congressman Waxman, he did assist greatly in the development of food and drug and other health care legislation.

And I have great respect for you, Bill. And we're glad to have you here and welcome you here.

Second, we'll have David Beier.

David, we're glad to see you again and glad to have you helping us on this committee.

David is the senior vice president of global governmental affairs for Amgen. Mr. Beier was former Vice President Gore's chief domestic policy adviser. And prior to that position, he was the vice president of government affairs and chief lobbyist for the biotech company Genentech, where he developed expertise in intellectual property, taxation, health care and other issues. Mr. Beier also worked for the House Judiciary Committee under former Congressman Pete Kastenmeier of Wisconsin.

We're delighted to have you here. And I've appreciated your advice through the years.

Our next witness is Dr. Carole Ben-Maimon. I think I'm pronouncing that right, Carole. She's the president and chief operating officer of Barr Research.

Dr. Ben-Maimon is responsible for all aspects of Barr's proprietary product research and development activities. She is also responsible for managing the company's expansion into biologics. Prior to joining Barr in 2001, Dr. Ben-Maimon served as senior vice president for science and public policy North America for Teva Pharmaceuticals USA,

where she coordinated Teva's U.S. and Canadian research and development efforts, product selection and global integration.

Dr. Ben-Maimon joined Lemmon, owned by Teva, in 1993 and served as vice president of medical and regulatory affairs from 1991 until 1993. Dr. Ben-Maimon was director of clinical pharmacology with Wyeth-Ayerst Research.

So we're grateful to have you take the time to be with us as well.

The final witness on this panel is Dr. Bill Hancock. Dr. Hancock is Bradstreet chair in bioanalytical chemistry, Barnett Institute and Department of Chemistry and Chemical Biology of Northeastern University in Boston, Massachusetts. Prior to joining Northeastern University, Dr. Hancock was the editor and chief for the "Journal of Proteomic Research" of the American Chemical Society. He was also the director of analytical chemistry at Genentech and a visiting scientist at the FDA in the mid 1980s. Dr. Hancock has received numerous awards and honors, including the American Chemical Society Award in Separation Science in 2003 and the Martin Gold Medal in Separation Science in the year 2000. Dr. Hancock has contributed to numerous industry publications and organizations.

The good news is this hearing is a unique opportunity to see a former Gore domestic policy adviser debate a former Nader disciple. The bad news is that our topic is so esoteric that only a handful of people listening will have any idea what they're talking about.

(LAUGHTER)

Of course, that's not unusual for those two candidates anyway. I'm only kidding.

Seriously, I look forward to hearing all the witnesses' testimony today. And look, we're very grateful that you've taken time to come and help us to understand these things better on the committee.

This is an area where we all need to work together in the best interests of our people and of people throughout the world. Because if we're successful in this area, we may very well be able to transcend into anything we do up until now.

So we'll start with you, Mr. Schultz. We'll go to Mr. Beier and then Dr. Ben-Maimon and then finally wind up with Dr. Hancock.

SCHULTZ: Thank you very much, Chairman Hatch. I appreciate this opportunity to testify on behalf of the Generic Pharmaceutical Association, the trade association whose 120 members produce more than 90 percent of all generic drugs in the United States. And I guess we owe our existence to you and to the Hatch-Waxman Act, which was passed 20 years ago and which has been such a tremendous success.

In 1984, we were at a crossroads. The brand industry was flourishing and yet FDA had no regulatory pathway and no system which provided for generic versions of most of these brand products. So even after their patents expired, they continued to sell their products at monopoly prices because they had monopolies. Congress responded and enacted the very successful Hatch-Waxman Act.

Today we are at a similar crossroads, Mr. Chairman, only this time it's for what we call biopharmaceuticals as opposed to the traditional pharmaceuticals. As you said in your opening statement, biotechnology products account for something like $33 billion in pharmaceutical sales, and the sales are growing. Many of the large selling biotech drugs have come off patent already or they will soon. And more importantly, in contrast to the traditional drugs, these have exceedingly high cost, in the thousands of dollars per patient per year. And so, the potential savings and the stakes for the health care system are enormous.

It's also significant that other countries are actively implementing such a program, including countries in the E.U., Asia and Latin America. In fact, the E.U. issued guidance three years ago to assist the industry in bringing generic biopharmaceuticals to the market. As the world leader in pharmaceutical development, the U.S. should be willing to also take on a leadership role in the development of a viable framework for generic biopharmaceuticals.

I now would like to address several specific questions. First of all, does the FDA have the legal authority to approve generic biopharmaceuticals? We believe the answer is clearly yes. As explained in my testimony, the FDA can adjust data requirements for generic biopharmaceuticals.

Second, if the FDA can act in this area, is there any need for Congress to do so? The answer here is yes as well. FDA, left to its own accord, could take years to resolve the questions of its legal authority and to promulgate

regulations. And years of litigation will follow that inevitably. Our health care system cannot afford to lose this precious time, especially given the fact that there are, as you said, already 150 biopharmaceutical products on the market, with more to come in future years.

It's just like 1984, Mr. Chairman. Congress needs to step in. It's appropriate for it to do so.

Third, should Congress wait for all the scientific issues to be resolved before it acts? This seems to be some of the industry's argument. The answer here is no.

As former Commissioner Mark McClellan recognized this year, and this is a quote, "We do believe that the science may be adequate now to proceed on several relatively simple biologics."

In other words, Mr. Chairman, the science is already there for some biologicals. In my written testimony we've given examples of where FDA has already reduced data requirements for certain biotech products that match ones previously approved. It may be sometime before it can do this for other products, and yet Congress should give FDA the legal authority and the direction to solidify a generic biopharmaceutical approval program.

For each product, it will be FDA, not Congress, that will be charged with determining what the approval criteria will be and what will be necessary to support our generic product. Simply put, sound science must drive the system, but there's no reason to wait to legislate in this critical field.

There's one telling example, which by itself rebuts the brand companies' argument that interchangeability between the generic and the brand is not possible. GlaxoSmithKline sells a Hepatitis B vaccine called Engerix-B that's made through biotechnology. Merck sells a similar product called Recombivax-HB. The FDA-approved labeling for both products states that these vaccines are interchangeable with each other and that either may be used to create the vaccination course initiated with the other. Importantly, FDA has allowed this interchangeability to be established without anything like a full set of data.

Fourth question, would it be unconstitutional for FDA to rely on the brand drug's approval? Would it be a taking of property without just compensation? Don't worry, I'm not going to spend the time that's really needed to engage in a constitutional debate here. And the association will be submitting shortly an analysis of this issue.

But I believe that it's clear from the Supreme Court jurisprudence in this area that the court has gone nowhere as far as is often claimed by the industry. Government agencies rely on information submitted by companies and permit other companies to rely on agency action based on this information all the time.

FDA, for example, regulates food additives by regulation. So a company submits its data, FDA issues a regulation, and the next company can rely on that regulation to get its approval. Of course, it has to wait for patents to expire and other intellectual property protection, but he can rely on the approval. It's not taking the data. It's relying on the approval.

We have a similar system for over-the-counter drugs. We have a similar system for medical devices. The first company gets its approval. If the second company is substantially equivalent it can get its as well. So these systems have been in place for many, many years, and no one's ever argued there's an unconstitutional taking.

Fifth, what should the regulatory system that permits FDA to approve generic biopharmaceuticals -- what should such a system look like? There are several important parameters.

First, the system needs to allow FDA the flexibility to tailor preclinical and clinical data requirements for biopharmaceutical products. The complexity of these products varies along the continuum. Some are very close in complexity to chemical drugs and some are much, much more complex. And FDA should have the authority to establish the appropriate requirements based on a scientific risk- benefit approach. Congress needs to, however, require FDA to impose only those regulatory requirements that are necessary to ensure safety and efficacy.

We faced this issue in 1984. There was a lot of concern that FDA would over-regulate. Congress was very careful in this statute and was very successful in ensuring that didn't happen. This is something to keep in mind here. But we want full regulation to ensure safety and efficacy.

We would urge Congress to direct the FDA to be very active in advising generic companies about how to comply with study design, data requirements and other issues. And we would urge Congress, once it enacts legislation -- and I believe that it is inevitable that Congress will enact this legislation -- that Congress will periodically monitor FDA and perhaps require FDA to issue periodic reports back to Congress.

In conclusion, Mr. Chairman, we ask for your help. As a result of the 1984 Hatch-Waxman Act, the generic drug industry now includes highly sophisticated and substantially capitalized companies that are ready to enter this market. A significant number of today's biopharmaceuticals are ready for generic versions.

An effective and efficient generic biopharmaceuticals program will result in tremendous untapped cost savings to this nation's health care system. In other words, today the case for legislative action is as strong as it was in 1984. The problem demands your attention. We thank you for this hearing. And the generic industry stands ready to assist you in any way that we can.

HATCH: Thank you so much. I appreciate that excellent testimony.

Mr. Beier, we'll turn to you. Glad to have you here.

BEIER: Good morning, Chairman Hatch. On behalf of Amgen, the world's largest biotechnology company, I come before you this morning with a simple message. Put patients first, and sound policy will follow. We believe there may be a role for follow-on biologics in the marketplace if patient safety is assured and innovation is encouraged and protected.

Every day over 80 Americans discover that they have leukemia. In the past hour, 150 Americans learned that they have diabetes. For each of these patients, there is only one issue before them -- hope for access to safe and new cures and treatments. The best and brightest hope for breakthroughs for these patients comes from the United States biotechnology industry. Almost half of the new medicines approved by the FDA last year were biological products, and over 300 biotechnology products are currently available in Phase III trials.

As Kenneth Shine, the head of the Institute of Medicine, said, "The 20th century was the century of physics and astronomy. The 21st century is going to be the century of biology and life sciences."

Let me be perfectly clear -- biological products are not the same as drugs. As the picture on the chart demonstrates, they are very different -- very, very different -- in terms of their size and complexity. Biological products are immensely more complicated to manufacture and therefore to reproduce by another manufacturer. That is why there needs to be a unique model for the approval of follow-on biologics.

My colleague Bill Schultz referred to 1984 and claimed that it was an analogous situation. In 1984, there were hundreds of profitable pharmaceutical companies, tens of thousands of drugs, and one-third of the leading 200 drugs were already subjected to generic competition. And the FDA had previously issued a scientific regulation outlining the circumstances for the approval of a generic product; 2004, there are 1,100 biotech companies. Only a handful of them make money. There are only 155 products on the market, and there is no regulatory pathway, no scientific basis for the approval of follow-on products until and unless a process like the one Commissioner Crawford outlined takes place.

As the FDA recognized this spring in its critical path report, which analyzed trends in drug innovation and development, there's a substantial risk that the promise of biological breakthroughs will not fully bear fruit, in part because of the increased complexity and expense of development. With these increased risks comes the need for strong incentives for innovation.

Mr. Chairman, as the author of Hatch-Waxman and as the supporter of innovation through other mechanisms such as orphan drug and pediatric exclusivity, you know firsthand the power of strong but fair patents, data exclusivity and trade secrets to spur investment, innovation and ultimately for breakthroughs for patients. As the Supreme Court said in the Bonito Boat case, the intellectual property system is a carefully crafted bargain, much like the one you crafted in 1984, Mr. Chairman.

This morning we start and end with patients. Patients benefit profoundly when there are balanced incentives to innovate. Patients are also benefited when they know after a complete public and science based process that medicines they take are completely safe and completely effective.

Current law does not provide the FDA with authority to approve follow-on biologics. We welcome the invitation from this committee to begin a dialogue about a regulatory pathway for follow-on biologics. We believe that Congress must protect innovation before the FDA proceeds with the first steps towards a rulemaking or even a public process leading to a guidance on science issues.

What do I mean by protection for innovation? In sum, it's the combination of patents, data exclusivity and trade secret protection. Billions of dollars of reasonable investment-backed expectations rest on the maintenance of these

rights. These rights benefit patients by promoting research and development for new breakthroughs. They protect the invention, usually in the form of a product patent, or often for biotech products the process. They also protect the preclinical and clinical trial data created by an innovator at the cost of hundreds of millions of dollars. This data exclusivity is an integral component of innovation protection.

Finally, the proprietary formulas, especially the detailed manufacturing specifications, are protected under federal law as trade secrets. As an innovator, Amgen does not seek to extend our legal rights beyond the meets and bounds of existing innovator protections. On the other hand, we would be concerned if the FDA seeks to rely on our proprietary data to approve a follow-on product.

To respond to Mr. Shultz's comments, it is true that the FDA in other analogous regulatory systems relies on the approval of other products. But he carefully noted they do not rely on the underlying data of the innovator. Our concern is about whether the agency would pierce our trade secrets and our knowledge of a manufacturing process and use that information to approve a follow-on product.

Finally, let me briefly address a topic not directly before the committee, that is, what are the appropriate regulatory rules that would permit the approval of a follow-on product?

In the main, we believe that preclinical data, clinical trials to demonstrate safety and efficacy and robust post-approval safety surveillance measures will be necessary. I stress these points because some of the other witnesses before you today indicate that they want to look to precedence in either China or Lithuania. Those systems do not have those elements and, in some instances, don't protect the intellectual property of the innovators.

While the exact standards for follow-on products will vary from product to product, there need to be some irreducible, minimum data standards before an approval can be granted. Why do we take this view? First, we believe that significant or major manufacturing changes in biologic products made by anyone, including the innovators, needs robust data submissions.

Second, because biologics, especially complex proteins, like the one outlined on the chart, are unique mixtures of active species. It is literally impossible for a second manufacturer to copy or duplicate the original product. Significant changes in cell lines and the manufacturing process to produce these products thus require a profound level of investigation, which can include preclinical and clinical data, before any reasonable regulatory authority can assess the safety and efficacy of these products.

In closing, we welcome this invitation and express our continued interest in working with you, Mr. Chairman, and the Congress and the FDA to fashion reasonable rules for the follow-on biologics, including the protection of innovator rights and measures to assure patient safety. Thank you.

HATCH: Well thank you so much.

Dr. Ben-Maimon, we'll take your testimony.

BEN-MAIMON: Thank you for having us. Thank you for inviting me here today.

My experience as a physician and in both generic and proprietary drug development provides me, I think, a unique perspective on the pharmaceutical industry. It really is this perspective that truly appreciates the value and contributions of the Hatch-Waxman Act. It also provides a perspective that makes me an advocate for a legislative process permitting the timely and efficient introduction of more affordable generic versions of biotech drugs.

BEN-MAIMON: The issues before this committee today are not unlike those of 20 years ago when Congress created a legislative pathway for efficient and timely approval of generic drugs. Indeed, many of the arguments opposing Hatch-Waxman are being made and will continue to be made during this debate, namely, that generic companies lack the scientific sophistication to operate in this complex arena, that it is impossible to adequately characterize the innovative products, and that the safety and efficacy of generic biotech products cannot be assured. I would like to assure you that this is not the case.

Today, I would like to make three points. First, America is at risk of losing its leadership position in biopharmaceuticals. Second, the science exists to support an abbreviated approval process. And third, the economics for generic biopharmaceuticals are compelling. And without them consumers will lose billions in savings while citizens of other countries realize the benefits of competition.

To say that generic biotech products cannot be made flies in the face of the facts. The truth is it's already being done in other parts of the world. Biogenerics are being developed, produced and sold in countries such as Poland, China and Lithuania. The loss of a leadership position threatens that other countries will be dictating standards for regulatory approval and the quality of the products that ultimately end up in the United States. In addition, American scientists will lose the opportunity for the high quality jobs that a robust American generic biopharmaceutical industry could bring to the United States.

The marketing of generic biotech products in other countries clearly demonstrates that products are comparable and that safety is not an issue. The exposure of thousands of patients without untoward effects demonstrates that these products are effective and safe.

There are also a number of biotech products that are already multi-source in the United States. Insulin and human growth hormones are good examples. Each of these products require full development programs. A generic biopharmaceutical approval process must not require generics to re-create unnecessary clinical and preclinical data.

The argument is made that biotech drugs are so complex that they cannot be characterized. This ignores the fact that advances over the past 20 years in analytical methods and validation techniques have allowed companies to characterize their biologic drug products such that the impact of changes in processes and cell lines can be evaluated and biologic drug products can be kept constant. The fact is, that generic companies are so no less capable than brand capable of applying state of the art science in manufacturing and product development.

The argument is made that there is a magic process. This may have been true when manufacturing processes were not validated and analytical methods were not advanced enough to characterize the final product. This is no longer the case. If it were, many of the products made by the various biotech manufacturers would not be available today. The regulatory system allows for the flexibility needed to make the necessary changes to processes and even cell lines required that enables them to supply these important drug products. In reality, biotech firms routinely justify process and site changes.

Finally, the need for generic versions of biopharmaceuticals is compelling. America's pharmaceutical biotechnology industry is one of the most successful and fastest growing segments of the U.S. health care system. Ten years ago, revenues for this industry were approximately $8 billion. According to IMS, the pharmaceutical biotech industry enjoyed in 2003 revenue growth in excess of 22 percent compared to 11 percent of the total market. By 2010 analysts estimate the biotechnology product sales will exceed $60 billion.

Generic competition is essential to control costs and to continue to stimulate innovation. If Congress does not act now, Americans will continue to face escalating drug costs. We urge Congress to create legislation that will clearly define a pathway that enables FDA to review and approve generic biopharmaceutical products in a timely manner. We urge Congress to ensure that requests for FDA approval are based on science and FDA does not place requirements on generic companies to re-create already established science, thus resulting in significantly increased expense and limited access.

In summary, we recognize the investment made by the biotech industry and the need for them to recoup their investment. But as has been proven under the Hatch-Waxman Act, generic competition fuels future innovation. Now is the time to provide the balance of competition to keep America's biotech innovators strong and growing. Thank you.

HATCH: Thank you, doctor. We appreciate it.

Dr. Hancock, we'll take your testimony now.

HANCOCK: Chairman Hatch, I'd like to thank you very much also for the opportunity to appear here and to discuss these very interesting and challenging scientific issues.

At the onset I'd also like to apologize that with the short notice I had and with the complexity of the issues I did not submit a full testimony, but I am willing to update that after the hearing in such ...

HATCH: We'll be happy to have you do that.

HANCOCK: Great.

So now, when you introduced me you went through some of my career. And I think I've been fortunate, that I've been able to experience academia and the biotechnology industry in the early days and then the instrument companies,

Hewlett-Packard and Thermo Electron, because I was interested in devising new analytical instrumentation. And now I've closed the circle. I'm back in academia. So I've really seen the issue from all sides, as it were.

So now in this situation, I'm well aware that discussing the technology can become very eye glazing. And so, rather than descend into the detail, what I'd like to do is just to go through some of the issues and experiences that can illustrate the complexity of generic biologicals in the follow-on products.

I was actually interested to note that one of the colleagues here used aspirin as an example of small molecule, but I've actually also chosen that too, perhaps subconsciously with the thought that the complexity of this issue is it leave us all with a headache. But we'll see what happens.

If we compare aspirin with, say, insulin, the smallest of proteins, we see within insulin that it's a much more complex molecule. And a change in a single amino acid can result in diabetes. So very subtle changes can have profound medical effects. And this is true much more so as we go to even more complex proteins.

Also, we notice that certain proteins are species-specific, again showing that one amino acid can make a total difference in the activity of the protein. Then I mentioned the composition that, OK, biologics can be composed of millions of atoms versus, say, 60 or 100. So when I was at Genentech, we characterized Activase and we showed that Activase contained 300,000 different molecular forms. So although Activase was pure, what we were faced with was producing Activase as a constant or consistent mixture that had desirable and effective properties in the patient. But it was a very complex mixture. And that was produced in mammalian cells.

If we move on to manufacturing and product quality, obviously biotechnology different. Rather than doing a chemical synthesis, we'll take typically an insertion of DNA into bacterial mammalian cells, and that's our manufacturing process.

Now, at Genentech we were proud that we took growth hormone and we forced e-coli to produce 25 percent of its protein as growth hormone. Over one quarter of that -- of the cell was growth hormone. Now the bacteria was unhappy with that situation. It fought back. It would get rid of the excess gene. It would mutate it. It would try and bring back the level of growth hormone. So nature does fight back, and that's true for all these engineered cells. So it requires the manufacturer to be on top of what's going on in the test tube or fermenter, as it were.

So I think as a general comment here what we rely on is that the manufacturer puts in a lot of very good quality science in process and then of course that the FDA very well regulates it, to check that the company is really controlling all of these things.

Then the area of quality and good manufacturing practice, as an example here I'd like to note, of course, that blood is a biologic. And so, while we don't use blood as a raw material, many of the raw materials to make the cell grow well are from a complex source. And so, there are issues of virus contamination, the BSE scare, prions, mad cow disease. These all remind us then that a natural source is not necessarily safe. And unfortunately, we continue to discover things, so we may discover new viruses so that a raw material that we think is safe today may not be in future. So again, we need good science and good, I think, regulatory interactions to consistently stay on top of things.

I think we're looking at manufacturer in an international perspective. So for example, a drug may be manufactured in Europe. And we notice that water, for example, in Europe is different from here. And so, I could go on with these different things. But I think the issue is that the process is very important here. We must regulate the process. We cannot just do it in final product testing.

I also note that product variance can be recognized by the immune system in the body. So for example, again a diabetic may have some function of their pancreas. So they have some function, they get a boost through insulin. If we have product variance, the immune system can produce antibodies to insulin and destroy the remaining pancreas. So we've actually made the patient worse rather than better. And of course, you can have other situations where there is immune disease.

So in conclusion, I'd like to note, then, that there are major unresolved scientific hurdles I think presently and in the near future, that's going to require a very close cooperation continuing between the manufacturers and the regulatory authorities, that we are going to need animal testing and clinical trials so at the end of the day we don't get to the situation where there are a surprise in the market.

Because I think ultimately, if we don't do our job well, that is, in the analytical and production and the testing, it is the patient population that will be the final tester. And we'll pick up the side effects when the product is marketed.

So I encourage the committee to then consider this interaction between the FDA and the regulators. Currently we do have a very strong process with full testing for a new drug approval. And so, I think as we move forward, it's important that this is not diluted, but that science and regulation continues to be very strong. Thank you.

HATCH: Well, thank you. I thank all of you for your testimony here today.

Let me start with you, Dr. Ben-Maimon. On average, how much will consumers save in the cost of pharmaceuticals by the presence of generic biologics?

BEN-MAIMON: I think it's -- as stated earlier, it's difficult to quantify. And I think it was a very good point that was made by Dan Troy that really it depends on how many companies can enter the marketplace.

I think what's significant is when you look at the generic drug process the savings are really reaped in two very specific areas, first in the area of R&D, where the pathway is abbreviated enough that the investment is more limited. And obviously then what needs to be charged at the other end can be substantially decreased.

I think the second is in the sales force. Generic companies sell essentially to pharmacies and wholesalers, whereas the brand industry promotes their products to doctors who are all over the country. And today there really are a limited number of chain drugstores and wholesalers. And so, whereas a generic company can have a sales force of maybe 10 sales reps, a brand company can have thousands of sales reps visiting doctors. And that translates ultimately into cost savings because obviously cost of promoting the products is less.

And so, I think that as the process is constructed, the savings are substantial. Even though the investment will probably be greater initially for generic companies to get into the biotechnology area, the savings will be substantial. And people have estimated that the prices will be at least 50 percent. But again I think that depends a lot on how many other companies are out there.

I would also say, Senator Hatch, that early on, it may be more expensive than as we get through the process and the systems are in place.

Finally, I think it's important to note that even today Barr, for instance, is making and developing a vaccine for the Department of Defense. And so, some of the processes are already going to be in place at certain companies. And that should provide a saving to some extent as well.

HATCH: You mentioned that under the current system innovator biotech companies may make changes to the manufacturing process of a biologic and establish safety and effectiveness for efficacy without conducting a full-scale clinical trials by using what I think you referred to as a comparability protocol.

You suggested that companies manufacturing -- that manufacturing generic companies could use a similar process, namely, the use of surrogate markers under the comparability protocol to establish a safety effectiveness of the generic biologics.

However, when an innovator company makes changes to the manufacturing process, they also have access to the original cell chain. Companies manufacturing generic biologics, on the other hand, do not, which seems to me a problem. And given that the production of biologics is dependent on a number of variables, including the manufacturing process and the host cell chain, how could the producer of a generic biologic ensure that the product is safe and effective, given the number of variables that differ from the production of the original biologic, without conducting new clinical trials?

BEN-MAIMON: I think it's an important point. And I think it's essential to recognize that as a physician, safety and efficacy are critical. And I think the generic industry is just as committed to the safety and efficacy of its biotech products as it already is to its generic drug products.

And I also think we have to differentiate between post-approval changes and pre-approval changes. When you talk about prior to approval, I think the generic industry -- and I'll speak for Barr and not for the generic industry. But at least at Barr we recognize that there will be some clinical trials required. And clearly, this will vary depending on the complexity of the product.

But what is submitted to the agency is a package of information. And it should be reviewed and evaluated as a package. There will be multiple analytical methods, multiple assessments of the actual molecular structure, and, again, comparability, and then, with all likelihood, depending upon the product, will need to be some clinical trials done. But I would venture to say that they could be done on surrogate markers such as hemoglobin, white blood cells, glucose,

rather than actually trying to re-create the wheel and looking at long-term morbidity and mortality, as some of these other products were, early in the development programs for the innovator.

And so, I think what we're asking for is a process that could be put in place that would allow us to discuss the requirements with the agency on a product-by-product basis, that would look at each product as a continuum, as exists in generic drugs today. I mean, it's a continuum, from the very simple to the very complex in the drug area as well as in the biotech area. And really the differentiation shouldn't be whether it's a biotech product or a drug but how complex that product is and what the requirement should be to ensure that it's safe and effective.

HATCH: I noticed Senator Schumer is here. Let me just ask -- I'll finish this question with you and then I'll turn to Senator Schumer, who would like to make a statement, and then I'll -- I have questions for each of the rest of you as well.

Dr. Ben-Maimon, you stated that you believe some products have been misclassified under the PHSA and that they should be rightly classified under the Food, Drug and Cosmetic Act. Given that 351 of the PHSA currently speaks to the approval of biologics, what products or, rather, what type of products do you believe we misclassified under the PHSA? And also, why do you believe that the Food, Drug and Cosmetic Act should govern the approval of biologics?

BEN-MAIMON: I'm not an attorney, so I'll speak as a physician reading the language in the law, which may not be the appropriate way to do things, but that's the only position I can come from.

HATCH: OK.

BEN-MAIMON: The broader of the two laws is the FD&C Act. And it's clear that at least for manufacturing requirements and GMPs and a lot of the manufacturing changes and even now today with the merger of CDER at Food & Drug (ph), the FD&C is the broader of the acts and applies to -- and I think that it was stated by FDA this morning that a drug -- that biotech products actually qualify as drugs, even though the counter may not be true.

In addition to that, when you look at the PHSA Act, it is very clear from the language that they're talking about viruses, products that induce antitoxins, products that induce immunogenicity or allergens, and then there's this term, sort of, and analogous products.

Biotech drugs are -- at least the ones that we're talking about today, are the products that are made through recombinant technologies. And those products really are not viruses. They're not antitoxins. They're not arsenic. They really don't meet any of the very specific definitions listed in that definition in the legislation. And they have been sort of put there under analogous products.

And so, I just question whether that was a convenient place to have put them rather than really where they belong, and whether they really belong in the drug arena because they really act and perform as drugs and that FD&C regulates them as well.

BEIER: Mr. Chairman, can I comment on that question?

HATCH: Sure.

BEIER: I think the attempt to read the Public Health Service Act in that manner is frankly wrong. The FDA has construed the term "analogous" to include biotech products for more than 20 years. And to suggest an abrupt change of this nature would likely be struck down by courts as not having gone through the appropriate process. Be glad to submit something for the record on that question.

HATCH: That'd be fine, thank you.

I'm going to turn to Senator Schumer for his statement, and then I'd like to get back to the final questions I have.

SCHUMER: I have questions as well, Mr. Chairman, but I'll defer those to after yours.

HATCH: OK.

SCHUMER: But thank you, Mr. Chairman, for holding this hearing on an issue that I care a great deal about, and many of us do, and that is affordable **biologic medicines.**

As everyone knows, in 1984, Chairman Hatch, you authored a piece of legislation which has proven to be one of the most pro-consumer laws in our time. Hatch-Waxman helped millions of people save billions and billions of dollars on prescription drugs over the past two decades. And, of course, I've been actively involved in making it stronger.

I believe that biologics are the next frontier in our desire to make generic drugs as widely available as possible, to make cheaper drugs as widely available as possible.

In recent years we have had lots of changes. And biologics are a $30 billion industry. They account now for 12 percent of the total of pharmaceuticals. And the industry is growing at 20 percent, so every year they increase their percentage of the drug market.

And this is where we should be placing our focus now. Products with $10 billion in sales are expected to come off patent in the next several years. And that presents a real opportunity.

And the bottom line is, from the perspective of those of us who fought for improvements in the generic drug law, **biologic medicines** are no different. While the biotech industry benefited from patent restoration side of Hatch-Waxman, the law did not explicitly set up a fast track generic approval system for all biologics at that time because the industry was so new. Well, it's no longer new. Patents have been extended. And we ought to get to work on it.

And that's why I'm so glad, Mr. Chairman, that you have held this hearing.

Now, obviously there are differences between chemical drugs and biologic drugs. Biologic drugs are extremely complex and expensive to produce. Patients who use them spend tens of thousands of dollars a year for a single treatment, with the most expensive therapy costing around $200,000. But they are critical in many instances. They're lifesaving drugs treating diseases like cancer and diabetes and MS and rare diseases. And the technology holds the promise of finding cures for things like Alzheimer's disease and Parkinson's disease. But even more than in the chemical drug area, the exorbitant cost of the drugs often means that people can't afford to take them.

SCHUMER: Though the world of **biologic medicines** is an extremely complex business, we have no choice but to seize this opportunity to do the right thing for consumers, to find a way, using cutting edge science, to ensure that safe, affordable alternatives are brought to market as soon as possible. And of course, we have to find a way to do this without cutting innovators off at the knees.

Companies are already marketing safe and effective and affordable biologics in Eastern Europe, Russia, Asia and Latin America. They're not yet available in the E.U., which has a system of drug regulations similar to ours, but the E.U. has issued guidance on how biologics could be done. They issued that several years ago, and they are well on their way to approving several follow-on biologic products.

So unfortunately, in this area America lags sadly behind many other countries. Surely if the science is adequate to produce these products elsewhere, especially in Europe where the system of regulation, as I mentioned, is similar to ours, we can do it here. So we've got to get the process rolling.

I was encouraged by what seemed to be an eagerness on the part of the FDA under Commissioner McClellan to issue a draft scientific guidance to begin to lay out what is known and what is not known about the science of producing affordable biologics. But unfortunately, the process may be slowing.

And I have some questions for the FDA. I couldn't be here. I had a conflict. But I'd ask unanimous consent to submit them in writing and get them to answer them.

HATCH: We've allow ...

SCHUMER: Great.

HATCH: ... you have until the end of the day.

SCHUMER: We hope the process is not slowing, but it seems it has in the FDA. Certainly part of this process should be a vibrant public debate. But the FDA's done a whole lot of thinking on the science behind this. And the agency should issue its guidance now so we can get going on the drugs we do know something about.

With biologic drugs being extremely complex, it is my understanding that there is still a full spectrum of complexity among marketed products. There are some that are easier to do and some that are harder to do. And you don't have the solve the most difficult problem before getting guidance on some of the easier problems.

The FDA has said it has the authority to approve the follow-on products for those drugs that were originally approved under the Food, Drug and Cosmetic Act. And some of these drugs are less complicated on the spectrum.

We may not be able to jump headfirst into this with a one-size- fits-all system that works for every drug on the market. But we've got to begin somewhere. And we've got to begin now. And I hope this hearing will prod the FDA to move forward more quickly.

And I thank you, Mr. Chairman, for holding it.

HATCH: Thank you, Senator.

Mr. Schultz, in your testimony, you refute many of the arguments made by the brand name companies, that they've expressed in opposition to a system for the approval of follow-on biologics, such as that it would amount to a taking of their property without just compensation.

You also state that you believe that the FDA currently has the legal authority to approve generic biopharmaceuticals. And we all agree this is one of the great strengths of this country is the innovation in the health care industry.

Now, how would you envision maintaining incentives for innovation in the biotechnology industry?

SCHULTZ: Well, I think the first question is to look at the incentives that are there, the patent system and so on. The products that are coming off patent, just roughly looking at it, they have been on the market for 10, 12 or more years.

And the question is, is there some problem in terms of their profitability. Just looking at it very roughly, I think there's a very strong case that the incentives are already there. And once the products have been on the market for the period of the patent life, then when the patents expire, they ought to be available for generics.

Obviously, the brands are free to make a case that there are inadequate incentives, but I don't hear them making it. I don't hear them making that case.

HATCH: I'll ask the same -- I'll ask this series of questions to both you and Mr. Beier. And if you'd care to comment.

BEIER: Mr. Chairman, the existence of incentives to support risky inventions is something that you know firsthand. You know that because you were the author of the orphan drug exclusivity and, working with colleagues like Senator DeWine, pediatric exclusivity.

So the opportunity to use market forces to procure capital, that is, investments in startup biotech companies, is a profound one. The United States has 1,200 biotech companies. About 30 percent of those are publicly traded. But as I indicated before, a overwhelming majority, well over 90 percent of those companies, lose money every year. They make massive investments in R&D.

The way in which their investments are protected is a combination of three things: patent protection, data exclusivity and trade secret protection. Let me go through them in a series.

First, with respect to patent protection, as Senator Schumer noted correctly, the biotechnology industry is covered in part by Hatch-Waxman, but it is not covered with respect to process patents. And as a result, none of the patent listing or the litigation protections and procedures that were altered by Senator Schumer and Senator McCain and others last year apply to the biotechnology industry.

The second way in which the biotechnology industry has innovator rights is data exclusivity, that is, the rights they have in the case report forms and other clinical data. The question that's posed before this committee and ultimately the whole Congress will be what are the rules with respect to that kind of data.

And then the third kind of exclusivity is trade secret protection, usually contained in the CMC section of an application to the FDA, that is, the cell lines, the master cell lines, the fermentation methods, all the process quality steps that are necessary for complex proteins. That third category of information is hugely important, and a subject of a lot of investment by biotech companies.

So when Mr. Schultz says it's fine when the patent expires, that you can use all the data, I think that doesn't answer the complete question. You have to look at the other components, both data exclusivity and trade secret protection.

And let me also make one other point. I'd like to submit for the record some rebuttals to Mr. Schultz's comment about OTC and food additives, because I don't think they're particularly apt in this case.

HATCH: Without objection, we'll take that in the record.

Let me just ask both of you this question. The recent example of pure red cell aplasia, which is associated with the use of EPO, excuse me, erythropoietin. Is that the way you pronounce it?

BEIER: EPO is good enough for me.

HATCH: EPO is good enough for me too. But this highlighted a number of antibody-mediated reactions associated with biopharmaceuticals.

The cause for this serious side effect appears to be due to a subtle change that occurs during the manufacturing and reformulation process or in the handling and distribution process.

Now, it's now clear that nearly all biopharmaceuticals induce antibodies with the possibility, as mentioned by Dr. Hancock, of these serious immune reactions by two mechanisms, the classical reaction and the new mechanism of breaking immune tolerance. Now, how does this great risk attributed to a subtle change in the molecule due to a manufacturing or formulation change affect the issue of ensuring patient safety in the manufacture of generic biopharmaceuticals?

BEIER: Mr. Chairman, I think the best place to start is, we looked at the public domain literature on manufacturing changes. It's important to make a distinction between manufacturing changes made by a company that has access to the trade secrets and the manufacturing data, that is, an innovator company making changes to their own process is quite a different thing from a follow-on company who would be necessarily using a different cell line, different fermentation, a whole series of other things.

If you look at the publicly available literature, the potential safety risks for patients include immune response that you've noted with respect to the EPREX situation in Europe, potential allergic reactions, differences in glycosylation, that is, the sugar residues around the products, and a decrease in potency.

These changes can result from either changes in manufacturing sites or methods, changes in cell lines, changes in excipients, changes in storage or in transportation, or in scale up differences between manufacturers. All of those things need to be taken into account, because for complex proteins the FDA is regulating not just the product but the process of manufacturer.

So as the FDA proceeds with the science-based effort that they've got underway with DIA, they're going to be looking at manufacturing experts, academic experts, and we fully expect to cooperate completely with them, as we are with European regulators, in providing our best professional judgment about what's necessary to assure patient safety.

SCHULTZ: Could I comment? The FDA is charged with regulating a wide range of very, very tricky products. And it every day is making these important scientific decisions.

And this is true for the first biological to come on the market, just as it will be true when the second one and the generic one comes on the market. But this is why it is so important that in the legislation Congress give the FDA the flexibility to make the right scientific decision. And I think it's important, whether you're talking about the brand product or the generic.

Dr. Ben-Maimon actually knows something about this science, and she wanted to comment on this as well.

BEN-MAIMON: I think in this situation, it's exactly what I spoke about before. You have to separate post-approval changes from pre- approval changes. And in this situation the changes that you're referring to occurred after approval and may very well have -- should have required additional work.

There were also changes, as I understand it, in the formulation itself, with the deletion of what probably should've been considered a major component.

Quite honestly, this whole issue of the processes, the product, is essential from the standpoint of the biotech industry. But the generic industry and the drug industry is actually much more experienced and much more sensitive to changes in formulation that ultimately impact things like stability.

And so, I think when you talk about biotech generics and you're talking about pre-approval issues, you will have clinical data in the application that will have been discussed and worked out with the agency to allow you to look at the safety and efficacy of the product at the time of approval. What occurs post-approval is dictated by all kinds of

regulations, with prior approval and 30-day -- and you've heard in some of the testimony that was written changes being effective and some others.

But clearly, prior to approval, whatever the development process is will be tested clinically in patients. And so, the agency will be basing its decision not on changes but on the data contained in the application, which is dramatically distinct from the EPREX circumstances, which happened post-approval.

HATCH: OK. Dr. Hancock.

HANCOCK: I just have a concern with this discussion, that it's made to sound easier than it really is. And so, the changes are so subtle that I think often even within the company one cannot quite understand what happened to the product when a particular resin or purification or whatever changed. So I just want to emphasize for the committee that these changes are very subtle and very wide-reaching and we need to be very careful as we move forward.

HATCH: Thank you, all. I appreciate -- I have a number of questions I'm going to submit in writing because this is a complex area. And I would appreciate your sending back your answers as quickly as possible. My time is up.

Senator Schumer, I've got to leave in about five minutes, so ...

SCHUMER: I'll be quick, Mr. Chairman. I'd first ask unanimous consent to submit a whole lot of questions in writing.

HATCH: Without objection.

SCHUMER: OK.

But for Mr. Schultz, again, it's my understanding that the FDA had planned to issue draft guidance this summer, laying out the scientific parameters relevant to the creation of follow-on biologics. Is that correct?

SCHULTZ: It was widely anticipated. That was my understanding, too.

SCHUMER: Right. OK. Now, it seems this guidance is being delayed and they're having this public symposium first. At least it seems to me that the FDA has tremendous scientific expertise here. They've already said they have authority to approve follow-on products, at least for some of the drugs. Wouldn't it make sense from your point of view and from the consumer's point of view for the FDA to issue its guidance now, so we can get going on products we know something about?

SCHULTZ: Particularly, since the guidance that it was going to issue was a draft for comment. I mean, it was going to be its first cut at it, and there would have been a public discussion anyway. Now I gather that's all being pushed back for a symposium.

SCHUMER: The discussion doesn't have a root, a basis. It sort of floats out there in the ether, I guess. Do you have any idea why they delayed it?

SCHULTZ: No, I don't.

SCHUMER: Do you or does anyone here?

No. OK.

Anyone disagree that the FDA should move forward now? I'm sure there would be some people, maybe at the ends of the table.

Dr. Hancock?

BEIER: I'll take the bait, Senator.

SCHUMER: OK.

HANCOCK: Well, I do represent the coast. Maybe it's the end of the table too. I've participated in the first consensus form of meeting the FDA held right at the beginning of biotechnology, which was the approval of insulin. And I really think it's a very good process. It brought together all the various biotech companies in the world at the time and international experts and I think drove the consensus together. And I really think that did speed up the FDA.

I can understand your concern for not having further delay, but I think the best way to speed things up is to hold this meeting quickly and for the FDA then to pass their comments on to you. I would really support that process.

SCHUMER: Right. But what would be wrong with doing it the inverse, as Mr. Schultz sort of alluded, put out their guidance first, then have the big discussion, because they're going to have to have comments anyway.

BEIER: Senator, I think the advantage ...

SCHUMER: Mr. Beier.

BEIER: The advantage to having a public forum before the issuance of a draft guidance is seen by the fact that the FDA frequently adopts that particular point of view. I'd be glad to submit for the record the 10 or more instances in which they've done this in the last 10 years. The most recent one was the issuance of a draft guidance on pharmacogenomics, an equally complicated scientific endeavor.

The opportunity for targeted medicine, like Gleevec and other things that we all celebrate every day, that bring cures to people with cancer, the development of this targeted therapy is of huge public health consequence. But before issuing the draft guidance, the FDA had several public forums, laid out all the appropriate scientific issues, and as a result, when they finally came out with the document it was more robust. There was a great consensus.

In the long run, consumers benefit by having confidence that the agency has engaged in a science-based, transparent, public process, not just that several people in Rockville or elsewhere have thought about something and issued a draft guidance.

SCHUMER: No one's disputing that. The question is whether they could've issued the guidance and then had some discussion based on it and then reacted to what the public had to say.

BEIER: The example, senator, is if you look at what's happened in the European Union, the European Medicines Evaluation Agency came up with guidances in December. The agency is now struggling because they did not have a public forum, did not bring in experts about what exactly it means on a particular product basis. So incomplete record can produce either unintended consequences or can place patients in a situation where they may lack confidence in the appropriate regulatory authority.

SCHUMER: Mr. Schultz, then Mr. ...

SCHULTZ: There's a famous quote from Samuel Johnson -- "Nothing focuses the mind like a hanging" -- nothing focuses the FDA like a directive from Congress.

This is where we were in the early '80s. The FDA was talking about an ANDA program. It would've been many, many years before it got there if it weren't for the '84 Hatch-Waxman Act.

This is where they were in the late '80s with regard to nutrition labeling. There again, Congress stepped in, and it got done.

And I personally believe that this really demands congressional attention if your desire is to ...

SCHUMER: You got it from me.

SCHULTZ: ... get it done.

SCHUMER: I agree with you completely, Mr. Schultz. And I'm going to focus on this and push the FDA to move forward, because I agree. Sometimes -- sometimes, not always, and who knows in this case -- having all these forums without anything concrete just leads to more forums and takes too long a time.

And I don't see the contradiction in having guidance and then having discussion and still solving the problems that Mr. Beier mentioned. You can get the last word from my questions, Dr. Hancock, because I'm always mindful of my chairman's schedule.

HATCH: He is never mindful of my schedule -- never -- not once in the whole time he's been on this committee.

(LAUGHTER)

SCHUMER: That's one of the nicest things he's said about me in quite a while.

(LAUGHTER)

HATCH: Actually, I've said one or two other nice things.

SCHUMER: Yes, you have. Yes, you have, Mr. Chairman.

Go ahead, Dr. Hancock.

HATCH: Actually, I appreciate my colleague. He's a very thoughtful, very aggressive, very hardworking colleague, and I appreciate him.

SCHUMER: Dr. Hancock?

HANCOCK: I realize that I'm between the committee and lunch. So I would agree and support Congress really pushing all of us to be very vigorous in this area. So I support that 100 percent.

But I would encourage you to give the FDA access to the international body of science. These are very difficult issues. I'm actually working with the Human Proteome Organization, like HUGO. And it's amazing when you have a group of international scientists together, what they come up with. So I think we would move faster by assisting the FDA with as much outside help as they can. And I think the academics and government scientists stand ready to do that.

Thank you for the last word.

HATCH: Well, thank you.

And let me just say, Mr. Schultz, I agree with you it is inevitable that there will be legislation with regard to follow-on biologics. It's my hope that this hearing today will be a help to build a solid foundation so that we can do the job here and that it'd be wisely done in developing that legislation.

And in that regard I would ask each of you and others in the audience as well and those who watch this on television to give us the best ideas you can so that we can proceed and get this all done.

Just finally, I just had one more question for you, Mr. Beier, that struck me as something I should ask before we finish, and then this'll be the last question.

You stated in your submitted testimony that follow-on biologics cannot be considered therapeutically equivalent to the innovator product. However, I'm aware -- how do you reconcile that argument with the 1995 FDA decision or finding -- I guess it was a finding regarding Avonex, which was a Biogen product for the treatment of relapsing forms of multiple sclerosis -- that two cell lines could be unique and yet comparable. That's the way I interpreted that.

BEIER: The testimony that I submitted indicates that we believe that follow-on products should not be therapeutically substitutable, which is you shouldn't have a patient on one particular product and then switch it to a follow-on product, because that may produce a different immune response so that's to answer your first question.

With respect to the specific case that you're talking about, it's a very highly unusual fact pattern involving an American company and a German company who collaborated...

HATCH: That was...

BEIER: ... who had a contract. Both companies had access to trade secret information and manufacturing data. The two companies then had a business disagreement and the submission of the data from one of the dissatisfied parties did rely on the data from the other company, but there had been previously access to this information. So I think it's a relatively unique set of circumstances that led to that particular approval.

HATCH: Well, thank you. I appreciate your comments on that. We'll submit some further questions in writing.

I think this has been a very interesting hearing. And I'm sorry, Dr. Hancock, that I ran out of time. I had some questions for you as well, but I'll submit them in writing. And I know that you'll more than adequately answer them.

We're very grateful to all of you. We've learned a lot here today. And we challenge all of you and others in the scientific community to help us with regard to what I propose will be follow-on legislation. Thanks so much. With that, we'll recess until further notice.

END

NOTES:
[????] - Indicates Speaker Unknown
[--] - Indicates could not make out what was being said.[off mike] - Indicates could not make out what was being said.

PERSON: ORRIN G HATCH (94%); ARLEN SPECTER (57%); JON L KYL (57%); JEFF SESSIONS (56%); MICHAEL DEWINE (56%); SAXBY CHAMBLISS (55%); JOHN CORNYN (55%); LARRY CRAIG (55%); EDWARD M 'TED' KENNEDY (54%); PATRICK J LEAHY (54%); DIANNE FEINSTEIN (53%); JOSEPH R BIDEN (53%); JOHN C EDWARDS (51%); RICHARD J DURBIN (51%);

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